

**Amendments to the Claims:**

1. – 4. (Cancelled)
5. (Previously presented) An antibody Fab' fragment in which both the interchain cysteine of C<sub>H1</sub> and the interchain cysteine of C<sub>L</sub> have been replaced by another amino acid and an engineered cysteine in the light chain constant region is covalently bonded to a cysteine in the hinge region.
6. (Previously presented) The antibody fragment of claim 5 wherein the light chain constant region comprises any one of the sequences provided in the SEQ ID Nos 16-20.
7. (Previously presented) The antibody fragment of claim 6 wherein the hinge region comprises any one of the sequences provided in SEQ ID Nos 1-11.
8. – 20. (Cancelled)
21. (Withdrawn) A method of producing an antibody fragment of claim 14 comprising:
  - a. treating an antibody Fab or Fab' fragment in which either the interchain cysteine of C<sub>H1</sub> or the interchain cysteine of C<sub>L</sub> has been replaced by another amino acid with a reducing agent capable of generating a free thiol group in at least one cysteine of the heavy and/or light chain constant region and/or, where present, the hinge; and
  - b. reacting the treated fragment with an effector molecule.
22. (Withdrawn) The method of claim 21 wherein step (a) further comprises reducing the covalent bond between the C<sub>L</sub> interchain cysteine and a cysteine in the hinge region.

23. (Withdrawn) The method of claim 21 wherein step (a) further comprises reducing the covalent bond between an engineered cysteine in the light chain constant region and a cysteine in the hinge region.
24. (currently amended) An antibody Fab or Fab' fragment wherein the heavy chain in the fragment is not covalently bonded to the light chain, said fragment comprising ~~at least two~~two or more effector molecules, wherein each effector molecule is a PEG ~~or a PEG derivative that is an  $\alpha$ -halocarboxylic acid or ester, an imide, a vinyl sulphone, a disulphide, or a maleimide~~ with an average molecular weight in the range from 5,000 to 30,000 Da, one said effector molecule being attached to the interchain cysteine of C<sub>L</sub> and wherein the interchain cysteine of C<sub>H1</sub> has been replaced by another amino acid.
25. (Previously presented) The antibody fragment of claim 24 wherein one of said effector molecules is attached to a cysteine in the heavy chain constant region.
26. (Currently amended) An antibody Fab or Fab' fragment wherein the heavy chain in the fragment is not covalently bonded to the light chain, said fragment comprising two or more effector molecules, wherein each effector molecule is a PEG or a PEG derivative that is an  $\alpha$ -halocarboxylic acid or ester, an imide, a vinyl sulphone, a disulphide, or a maleimide. ~~The antibody fragment of claim 24,~~ wherein one said effector molecule is attached to a cysteine in the light chain constant region and one said effector molecule is attached to a cysteine in the heavy chain constant region, and the two cysteines would otherwise be linked to each other via a disulphide bond if the effector molecules were not attached.
27. (Previously presented) The antibody fragment of claim 24 wherein the fragment is a Fab' fragment that contains a modified hinge region.
28. (Previously presented) The antibody fragment of claim 27 wherein the hinge region comprises any one of the sequences provided in SEQ ID Nos 1-14.

29. (Previously presented) The antibody fragment of claim 24 wherein the fragment is a Fab' fragment and an effector molecule is attached to at least one cysteine in the hinge region.

30. (Withdrawn) A method of producing an antibody fragment of claim 24 comprising:

- a. treating an antibody Fab or Fab' fragment with a reducing agent capable of generating a free thiol group in at least the interchain cysteine of C<sub>H</sub>1 and the interchain cysteine of C<sub>L</sub>; and
- b. reacting the treatment fragment with an effector molecule.

31. (Withdrawn and currently amended) The antibody fragment of claim 24 wherein the site of the interchain cysteine of C<sub>L</sub> is at position 214 of the light chain and the site of the interchain cysteine of C<sub>H</sub>1 is at position 233 of the heavy chain.

32. (Withdrawn) The method of claims 21 or 30 wherein the reducing agent is a non-thiol based reducing agent.

33. (Withdrawn) The method of claim 32 wherein the reducing agent is a trialkylphosphine.

34. (Withdrawn) The method of claim 33 wherein the trialkylphosphine reducing agent is tris(2-carboxyethyl)phosphine (TCEP).

35. (Withdrawn) The method of claim 33 wherein the trialkylphosphine reducing agent is tris(3-hydroxypropyl)phosphine (THP).

36. (Withdrawn) The method of claim 21 wherein either or both of steps (a) and (b) are performed in the presence of a chelating agent.

37. (Withdrawn) The method of claim 36 wherein the chelating agent is EDTA.
38. (Withdrawn) The method of claim 37 wherein both steps (a) and (b) are performed in the presence of EDTA.
39. – 41. (Cancelled)
42. (Cancelled)
43. (previously presented) A pharmaceutical composition comprising an antibody fragment of claim 24, together with one or more pharmaceutically acceptable excipients, diluents or carriers.
44. (Cancelled)
45. (currently amended) An antibody fragment according to claim 24, wherein said effector molecules are each ~~20,000~~ approximately 5,000– 40,000 Da or larger.
46. (currently amended) An antibody fragment according to claim 24, wherein said effector molecules are each ~~30,000~~ approximately 20,000 - 40,000 Da or larger.
47. (Cancelled)
48. (Currently amended) An antibody Fab or Fab' fragment wherein the heavy chain in the fragment is not covalently bonded to the light chain, said fragment comprising two or more at least two effector molecules, wherein each effector molecule is a PEG ~~with an average molecular weight in the range from 5,000 to 30,000 Da~~, or a PEG derivative that is an  $\alpha$ -halocarboxylic acid or ester, an imide, a vinyl sulphone, a disulphide, or a maleimide, one said effector molecule being attached to the interchain cysteine of C<sub>H1</sub>, and wherein the interchain cysteine of C<sub>L</sub> has been replaced by another amino acid.

49. (Previously presented) The antibody fragment of claim 48 wherein the fragment is a Fab' fragment that contains a modified hinge region.
50. (Previously presented) The antibody fragment of claim 49 wherein the hinge region comprises any one of the sequences provided in SEQ ID Nos 1-14.
51. (Previously presented) The antibody fragment of claim 48 wherein the fragment is a Fab' fragment and an effector molecule is attached to at least one cysteine in the hinge region.
52. (Previously presented) A pharmaceutical composition comprising an antibody fragment of claim 48, together with one or more pharmaceutically acceptable excipients, diluents or carriers.
53. (Currently amended) An antibody fragment according to claim 48, wherein said effector molecules are each approximately 5,000–40,000 ~~20,000~~ Da ~~or larger~~.
54. (Previously presented) An antibody fragment according to claim 48, wherein said effector molecules are each approximately 20,000 - 40,000 ~~30,000~~ Da ~~or larger~~.
55. (Currently amended) An antibody Fab' fragment wherein the interchain cysteine of C<sub>H</sub>1 has been replaced by another amino acid and the heavy chain in the fragment is not covalently bonded to the light chain, said Fab' fragment comprising:  
 two or three effector molecules, each of which is a PEG or a PEG derivative that is an  $\alpha$ -halocarboxylic acid or ester, an imide, a vinyl sulphone, a disulphide, or a malcimide, with an average molecular weight in the range from 5,000 to 40,000 ~~30,000~~ Da, and  
 a native hinge or a modified hinge containing one or two cysteines,  
 wherein one said effector molecule being attached to the interchain cysteine of C<sub>L</sub>,  
 and wherein any additional effector molecules are attached to the hinge.

56. (Currently amended) An antibody Fab' fragment wherein the interchain cysteine of C<sub>L</sub> has been replaced by another amino acid and the heavy chain in the fragment is not covalently bonded to the light chain, said Fab' fragment comprising:

two or three effector molecules, each of which is a PEG or a PEG derivative thereof that is an  $\alpha$ -halocarboxylic acid or ester, an imide, a vinyl sulphone, a disulphide, or a malcimide, with an average molecular weight in the range from 5,000 to 40,000 ~~30,000~~-Da, and

a native hinge or a modified hinge containing one or two cysteines,  
wherein one said effector molecule being attached to the interchain cysteine of C<sub>H1</sub> and  
wherein any additional effector molecules are attached to the hinge.

57. (New) The antibody fragment of claim 26 wherein the fragment is a Fab' fragment that contains a modified hinge region.

58. (New) The antibody fragment of claim 57 wherein the hinge region comprises any one of the sequences provided in SEQ ID Nos 1-14.

59. (New) The antibody fragment of claim 26 wherein the fragment is a Fab' fragment and an effector molecule is attached to at least one cysteine in the hinge region.

60. (New) The antibody fragment of claim 26 wherein one of said effector molecules is attached to a cysteine in the heavy chain constant region.

61. (New) An Fab' fragment wherein the interchain cysteine of C<sub>H</sub>1 has been replaced by another amino acid, and wherein the C<sub>L</sub> interchain cysteine is covalently bonded to a cysteine in the hinge region.